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Biosynthesis and regulation of secondary metabolites in microorganisms

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Secondary metabolites are organic compounds with complex chemical structures and diverse physiological functions. Secondary metabolites include antibiotics, pigments, and other bioactive compounds. Many of these compounds have important agricultural and medical applications. Microorganisms, especially actinomycetes and filamentous fungi, are noted as a rich source of bioactive secondary metabolites. Typically, each species produces several antibiotics, with the profile being species-specific.

Secondary metabolites are synthesized from their precursors through multistep biosynthetic pathways. In general, the genes governing the biosynthesis of secondary metabolites are clustered together, and an increasing number of gene clusters responsible for the biosynthesis of secondary metabolites have been discovered. The availability of clusters has accelerated functional investigations of biosynthetic pathways of secondary metabolites. A thorough understanding of the enzymatic process is required for metabolic engineering to improve production of secondary metabolites and for combinatorial biosynthesis to generate novel compounds or derivatives. Elucidation of the biosynthetic process requires knowledge from diverse disciplines, including bioinformatics, chemistry, and genetics.

Secondary metabolites are generally produced during the stationary phase of growth in microorganisms. The biosynthesis of secondary metabolites is a complex process involving cascade regulations, and these regulatory mechanisms have been investigated extensively at the transcriptional level. However, regulation could also occur at the pre-transcriptional and/or post-transcriptional levels. Pre-transcriptional regulation occurs primarily at the chromatin level (epigenetic regulation), while post-transcriptional regulation is achieved via small non-coding RNAs (sRNAs) and protein degradation machinery. Though still in its infancy, some interesting progress has been made in this field [1,2].

As antibiotics are the most important of the secondary metabolites, we will focus on antibiotics hereafter. The alarming rise in emergence and prevalence of antibiotic resistance poses a major threat to human healthcare. It is clear that novel antibiotics are urgently needed to combat this problem. However, the supply of new antibiotics has declined in the last decade [3]. To reverse this trend, several strategies have been devised to find or create new antibiotics, which we describe in detail below.

1 Generation of new derivatives

Based on results from extensive biosynthetic studies, selective inactivation of structural genes can produce new antibiotic analogs [4,5]. Mutasynthesis can be started by blocking the biosynthesis of key biosynthetic components, and a variety of alternative biosynthetic intermediates can then be fed to the mutant to produce novel antibiotic variants. Combinatorial biosynthesis takes advantage of similarities between the molecular structures of two or more antibiotics to generate hybrid compounds with improved properties [6].

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2 Design of new antibiotics by synthetic biology

By applying the engineering paradigm of systems design to biological systems, synthetic biology can generate unnatural compounds with predictable features. The successful application of this technology requires a diverse library of biological modules. These modules can be integrated to assemble complex pathways in a programmed fashion. The assembled pathway needs a suitable surrogate host for production, and *Escherichia coli* is the most commonly used [7]. Alternative hosts, like *Streptomyces*, have also been successful [8]. By using the well-developed hosts as a biological factory, we can produce new antibiotics through assembly of designed and compatible modules.

3 Activation of cryptic gene clusters

Advances in omics and bioinformatics have promoted the investigation of biosynthesis and regulation of secondary metabolites. Genome mining and scanning are frequently used to find new secondary metabolites. Sequencing of microbial genomes has revealed a large number of secondary metabolic gene clusters. However, most of these gene clusters are expressed inefficiently, or not at all, under standard culture conditions. Therefore, it is necessary to develop new methods and strategies to identify the physiological signals and regulatory mechanisms responsible for the activation of these "cryptic" pathways. Activating these clusters will open up new avenues for identifying novel and important antibiotics. The discovery of natural products by genomic-based approaches largely depends on the identification and annotation of secondary metabolite gene clusters through *in silico* analysis. Once these gene clusters are identified, various methods are needed for activating the expression of cryptic gene clusters. These methods include optimization of fermentation conditions, genome mining, ribosome engineering, genetic manipulation of the regulators controlling gene clusters, induction of signaling molecules, and heterologous expression of gene clusters in different host strains [9].

4 Novel antibiotics from marine microorganisms

Marine microorganisms exist in an environment that is very different from that of their terrestrial counterparts. They have to adapt to different conditions, and thus gain different metabolic capabilities. Marine microorganisms represent an untapped source from which novel antibiotics can be discovered. Since the vast majority of these microorganisms remain unculturable in the laboratory, metagenome libraries from a large number of marine samples are needed to access the genetic material of these species. Considering the high diversity of this genetic material, there is a greater chance of finding novel antibiotics.

This special issue is dedicated to the biosynthesis and regulation of secondary metabolites from microorganisms of terrestrial or marine origin. We would like to thank all authors for their contributions. We sincerely hope that this special topic will encourage scientists, especially young scientists, to work in this important field of novel antibiotic discovery, and to report their findings in future issues of *Science China Life Sciences*.

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Biographical Sketch

Niu GuoQing obtained his Ph.D. in microbial genetics in 2006 at the Institute of Microbiology, Chinese Academy of Sciences (CAS). After graduation he worked for four years as an Associate Research Scholar at the University of Oklahoma Health Sciences Center, USA. In 2010, he was appointed Associate Professor in molecular microbiology at the Institute of Microbiology, CAS. His research focuses on the molecular regulation of secondary metabolites in *Streptomyces*. From 2006 to the present, he has published 15 research papers.

Biographical Sketch

Tan HuaRong obtained his Ph.D. in microbial genetics in 1991 at the University of East Anglia, England. In 1992, he started to work on the molecular regulation of differentiation and secondary metabolites in *Streptomyces*. In 1994, he was appointed as a Full Professor in molecular microbiology at the Institute of Microbiology, Chinese Academy of Sciences (CAS). From1999 to 2008, he served as the Deputy Director of the Institute of Microbiology, CAS. From 2001 to 2011, he was a Vice President of the Chinese Society for Microbiology. From 2006 to the present, he has been an Editor in Chief for *Acta Microbiologica Sinica*. He has published more than 120 papers in his research field.